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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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ISIS PHARMACEUTICALS INC
1896 RUTHERFORD RD.
CARLSBAD, CA 92008

EXAMINER	
ASHEN, JON BENJAMIN	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 02/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/642,802	GRAHAM ET AL.	
	Examiner	Art Unit	
	Jon B. Ashen	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 21-23 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 21-23 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 8/03.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application

1. Claims 21-23 are pending and currently under examination in this application.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 22-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Instant claims 22-23 are drawn to "a compound 15 to 25 nucleobases in length." However, no disclosure could be located, in the specification as filed, of a compound of this specific size range. Applicant has contemplated, in the context of the invention, preferred size ranges of 8 to 50 and 12 to 30 nucleobases (pg. 12), but has not contemplated, in the context of the invention, the specific size range of 15 to 25 nucleobases, as now claimed. If applicant believes that support for the particular size limitation of 15 to 25 nucleobases is provided in the specification as filed, applicant should point out, with particularity, where such support is to be found.

4. Claims 21-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claims 21-23 are broadly drawn to a method of inhibiting the expression of complement component c3 in a cell (which reads on both *in vitro* and *in vivo* embodiments) by contacting a cell with an inhibitor which specifically blocks expression of complement component c3 (claim 21) wherein the inhibitor is a compound 15-25 nucleobases in length that specifically hybridizes to the coding sequence of a nucleic acid molecule encoding complement component c3 (claim 22) wherein the inhibitor is a chimeric antisense oligonucleotide or comprises at least one modified internucleoside linkage, sugar moiety or nucleobase (claim 23).

However, the specification as filed does not provide an adequate written description of the broad genus of the inhibitors which specifically block expression of complement component c3 or wherein said inhibitors specifically hybridize to a coding sequence of a nucleic acid molecule encoding any complement component c3, (including splice variants, isoforms and alleles; i.e., human complement component c3a and complement component c3b, for example) from any organism, that will function commensurate with the breadth of what is now claimed, to specifically block expression of complement component c3 or reduce the expression of complement component c3

mRNA (as required of a compound that specifically hybridizes or as an antisense oligonucleotide as claimed).

No definition or description of a generic inhibitor which specifically blocks expression of complement component c3 could be located in the specification as filed. The disclosure of the specification contemplates and exemplifies, in the context of inhibitors which specifically block complement component c3 expression, only species of the required inhibitors and compounds that are fully complementary antisense oligonucleotides 20 nucleobases in length and targeted to the coding regions of human and mouse complement component c3, *in vitro* (tables 1 and 2). The specification discloses no *in vivo* data. The specification states, in regards to the oligomeric compounds contemplated as inhibitors of the invention, "Thus, "specifically hybridizable" and "complementary" are terms which are used to indicate a sufficient degree of complementarity or precise pairing such that stable and specific binding occurs between the oligonucleotide and the DNA or RNA target. It is understood in the art that the sequence of an antisense compound need not be 100% complementary to that of its target nucleic acid to be specifically hybridizable. An antisense compound is specifically hybridizable when binding of the compound to the target DNA or RNA molecule interferes with the normal function of the target DNA or RNA to cause a loss of utility, and there is a sufficient degree of complementarity to avoid non-specific binding of the antisense compound to non-target sequences under conditions in which specific binding is desired, i.e., under physiological conditions in the case of *in vivo* assays or therapeutic treatment, and in the case of *in vitro* assays, under conditions in which the

assays are performed" (pg. 9). The specification discloses illustrative antisense compounds of the invention are preferably 8 to 50 or 12 to 30 nucleobases in length and include antisense oligomeric compounds, antisense oligonucleotides, ribozymes, EGS, oligonucleotides, alternate splicers, primers, probes, and other oligomeric compounds that can be single or double stranded nucleic acid molecules, oligonucleotide mimetics and analogs (pg. 12).

The specification thereby provides an disclosure of a broad class of antisense compounds that are claimed functionally but provides only a few narrow examples of species from within that broad class that are 20 nucleobase single stranded fully complementary antisense oligonucleotides. The specification provides no disclosure of the structure of any particular and functional inhibitor, from within the broad genus of claimed inhibitors, that is not a species of oligomeric compound as above. Moreover, no antisense oligonucleotide smaller than 20 nucleobases and less than 100% complementary to the target that remains sufficiently complementary so that it functions to be specifically hybridizable, commensurate with the breadth of what is claimed, has been disclosed, for example. In light of Applicant's disclosure above, it is clear that species of particular and functional antisense oligomers (oligonucleotides) must be derived empirically through the testing of each species, such that the function of specifically hybridizing to a given target while avoiding non-specific binding, wherein the antisense oligonucleotide can be "less than 100% complementary" to the target, is achieved.

In disclosing no guidance with regards to the broad genus of inhibitors as claimed which specifically block complement component c3 expression and only general guidance in regards to what is encompassed by the broad genus of compounds as claimed that are specifically hybridizable as claimed, the specification does not provide a correlation between the structure of the claimed inhibitor or compound and the function as claimed, that will inhibit the expression of complement component c3, *in vivo*. In the instant case, the state of the art cannot provide the required guidance, from knowledge of the primary nucleotide sequence of an mRNA, the particular structure of an antisense oligonucleotide as claimed, that would function, in vivo, commensurate with the breadth of what is claimed (see Agrawal et al. and Opalinska et al. as cited below).

Additionally, the specification as filed has not disclosed any distinguishing identifying characteristics of the broad genera of claimed inhibitors or compounds that are required to practice the instant methods, *in vivo*, as claimed. Therefore, Applicant has not provided a disclosure which indicates that they in possession of a representative number of species from within the broadly claimed genera of inhibitors and compounds that are required to practice the methods of the instant invention.

MPEP § 2163[R-2] I. states:

> To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See, e.g., > Moba, B.V. v. Diamond Automation, Inc., 325 F.3d 1306, 1319, 66 USPQ2d 1429, 1438 (Fed. Cir. 2003);< Vas-Cath, Inc. v. Mahurkar, 935 F.2d at 1563, 19 USPQ2d at 1116.
>
> The fundamental factual inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed. See, e.g., Vas-Cath, Inc., 935 F.2d at

1563-64, 19 USPQ2d at 1117.

Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., Pfaff v. Wells Elecs., Inc., 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406; Amgen, Inc. v. Chugai Pharmaceutical, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it").

An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. > Enzo Biochem, 323 F.3d at 964, 63 USPQ2d at 1613.<

In the instant case, Applicant has not provided adequate written description of their invention because the specification does not convey, with reasonable clarity to those of skill in the art, as of the filing date sought, that applicant was in possession of the invention now claimed. Applicant has not shown how the invention was "ready for patenting" such as by the disclosure of the structure of an inhibitor or compound as claimed, that would function commensurate with the breadth of what is now claimed (that shows that the claimed invention was complete), or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of a representative number of species from within the broad genera of inhibitors or compounds that are required to practice the instantly claimed methods.

5. Claims 21-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the instantly claimed methods, *in vitro*, using the

functional species of antisense oligonucleotides as disclosed, that are fully complementary 20 base pair single stranded antisense oligonucleotides, does not reasonably provide enablement for the full scope of the claimed methods of inhibiting the expression of complement component c3 *in vitro* and *in vivo* using the broad genera of inhibitors which specifically block complement component c3 expression or compounds that are specifically hybridizable to a nucleic acid molecule encoding complement component c3 (as above). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The following factors as enumerated *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), are considered when making a determination that a disclosure is not enabling: the breadth of the claims, the nature of the invention, the state of the prior art, the level of ordinary skill in the art, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples and the quantity of experimentation needed to make the invention based on the content of the disclosure.

The scope of claims 21-23 is broadly drawn and reads on methods of inhibiting gene expression *in vivo* and *in vitro* comprising administering any number of inhibitors which specifically block expression of complement component c3 or compounds (including chimeric or modified antisense oligonucleotides) that can be any compounds 15-25 nucleobases in length that are specifically hybridizable with a coding region of a nucleic acid molecule encoding any complement component c3 (i.e., from any organism

and including any splice variants, isoforms or alleles) wherein the claimed inhibitors and compounds inhibit complement activation or the expression of complement component c3. Additionally, the scope of the instant claims is reasonably interpreted to encompass *in vitro* and *in vivo* methods of treatment, particularly when viewed in light of the disclosures of the specification which contemplates methods of treatment using the claimed compounds (See, for example, pg. 4, line 35 to pg. 5, line 14).

The specification as filed, however, provides no support for claims drawn to methods of inhibiting gene expression or methods of treatment *in vivo* using the inhibitors and compounds as claimed. The specification as filed provides no examples of *in vivo* methods of gene inhibition or treatment comprising administering the claimed inhibitors or compounds no guidance as to how to make or use the claimed inhibitors or compounds of the invention that will function to provide the specified biological effect or treatment as claimed. The specification merely asserts that, "Further provided are methods of treating an animal, particularly a human, suspected of having or being prone to a disease or condition associated with the expression of complement component c3" (pg. 5). The specification also states that, "For therapeutics, an animal, preferably a human, suspected of having a disease or disorder which can be treated by modulating the expression of complement component c3 is treated by administering antisense compounds in accordance with this invention (pg. 26) and a general disclosure of the formulation of oligonucleotide compounds for administration in methods of treatment (pg. 53). However, the specification as filed provides no specific guidance with regards to how such a method of treatment would be practiced, such that the skilled artisan

could make and use the instantly claimed method *in vivo*, to achieve the claimed biological effect of inhibition or to achieve a treatment, as claimed.

The state of the art at the time the instant invention was made relative to the enablement of the antisense therapies *in vivo* recognized that there is a high degree of unpredictability in the art of applying antisense without direct evidence of a specific biological or therapeutic effect due to numerous obstacles that continue, to the present day, to hinder the application of nucleic acid therapies *in vivo* (whole organism). Such obstacles include, for example, problems with delivery (including uptake by cells) and target accessibility (see below: Agrawal et al., Opalinska et al., Jen et al.). At the time the instant invention was made and even many years later, such obstacles were still relevant to the enablement of antisense inhibition of gene expression *in vivo*.

In particular regard to methods which require particular *in vivo* treatments or biological effects, cell culture examples are generally not predictive of *in vivo* inhibition due to differences in metabolites and clearance rates, local concentration of antisense, and the potential for non-antisense side effects. The field of antisense generally, to date, does not provide guidelines by which antisense can be routinely targeted to generally any cell type *in vivo* (whole organism) at a concentration effective to result in a treatment effect. The following references discuss the problems of nucleic acid based therapies in reference to the claimed therapeutic antisense method.

At the time the instant invention was made, Agrawal et al. 2000 (Molecular Medicine Today, Vol. 61, pp. 72-81) indicate, in particular regard to antisense methods of treatment of cells *in vitro*, that, "*In vitro*, cellular uptake of antisense oligonucleotides

depends on many factors including cell type, kinetics of uptake, tissue culture conditions and chemical nature, length and sequence of the oligonucleotide. Any one of these factors can influence the biological activity of an antisense oligonucleotide. It is therefore appropriate to study each antisense oligonucleotide in its own context and relevant cell line without generalizing the results for every oligonucleotide" (pg. 80, col. 1, 1st paragraph). It is noted here that the same issues that have been outlined above in regards to *in vitro* enablement of antisense methods of treatment apply to the more complicated endeavor of applying antisense methods of treatment *ex vivo*.

In particular regard to antisense methods of treatment of cells *in vivo*, Opalinska et al. 2002 (Nature Reviews, Vol. 1, pp. 503-514) provide a review of the challenges that remain before nucleic acid therapy becomes routine in therapeutic settings and clearly indicate that the art of nucleic acid therapy remains highly unpredictable and unreliable, particularly *in vivo*. According to Opalinska et al., "Although conceptually elegant, the prospect of using nucleic acid molecules for treating human malignancies and other diseases remains tantalizing, but uncertain. The main cause of this uncertainty is the apparent randomness with which these materials modulate the expression of their intended targets. It is a widely held view that molecule delivery, and selection of which messenger RNA sequence to physically target, are core stumbling blocks that hold up progress in the field" (pg 503). Opalinska et al. also note that .. "[I]t is widely appreciated that the ability of nucleic acid molecules to modify gene expression *in vivo* is quite variable and therefore wanting in terms of reliability. Several issues have been implicated as a root cause of this problem, including molecule

delivery to targeted cells and specific compartments within cells, and identification of sequence that is accessible to hybridization in the genomic DNA or RNA" (pg. 511).

In regards to the delivery of therapeutic nucleic acids, Jen et al. (Stem Cells 2000, Vol. 18, p 307-319) state (pg. 313, second column, second paragraph) "One of the major limitations for the therapeutic use of AS-ODNS and ribozymes is the problem of delivery.... presently, some success has been achieved in tissue culture, but efficient delivery for *in vivo* animal studies remains questionable". Jen et al. outlines many of the factors limiting the application of antisense for therapeutic purposes and concludes (pg. 315, second column), "Given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive."

Therefore, in light of the references above, the specification as filed does not contain the specific guidance that would have been required, by skilled artisan, at the time the invention was made, to have practiced the claimed methods over the broad scope claimed because specification does not provide an enabling disclosure of the inhibitors or compounds that are required to provide the claimed treatment or specific biological effect, *in vivo*. In order to practice the invention as claimed, the skilled artisan would have needed, therefore, to have performed a vast quantity of undue *de novo* trial and error experimentation, in order determine how to make and use a method, *in vivo*, as claimed. This undue *de novo* trial and error experimentation would have included the determination of such factors as dosage, route of administration, kinetics of uptake, disposition of the inhibitors or compounds in cells, tissues or the organism to be treated, and the half-life and stability of the required inhibitors or compounds, *in vivo*. Given the

art recognized unpredictability of the application of antisense *in vitro* and *in vivo*, at the time the invention was made, this determination would not have been routine and would have required specific guidance. The specification does not provide this specific guidance for *in vivo* methods nor did the antisense field at the time of filing have such general guidelines.

Therefore, based on the nature of the invention as a method of *in vitro* and *in vivo* treatment, the degree of unpredictability in the art of antisense oligonucleotide therapy at the time the invention was made, the breadth of the claimed methods as a method of specifically blocking complement component c3 activation or inhibiting the expression of complement component c3 *in vivo*, the lack of guidance as to what particular species of inhibitors or compounds as claimed would be required to practice the method as claimed, the need to screen multiple species of said inhibitors or compounds so as to allow identification of particular species as functional within the method of treatment as claimed and the quantity of *de novo* trial and error experimentation necessary to discover the above, an undue amount of experimentation would be required in order to practice the method of treatment as claimed. Therefore, the inventors have not enabled one skilled in the art to make and use the method of the claimed invention.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 21-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over de Bruijn et al. 1985 (Reference AB, PTO Form 1449 filed 08/18/03 in this application), Carroll 1998 (Reference AA PTO Form 1449 filed 08/18/03 in this application), Taylor et al. 1999 (Drug Disc. Today, Vol. 4), Bennett et al. (U.S. Patent 5,998,148) and Baracchini et al. (US Patent 5,801,154) for the reasons of record as set forth in the Action mailed 6/17/05.

The invention set forth in claims 21-23 is drawn to a method of inhibiting the expression of complement component c3 in cells using inhibitors that specifically block complement component c3 expression or compounds that are specifically hybridizable to the coding region of a nucleic acid molecule encoding complement component c3

(including antisense compounds) wherein said antisense compounds are chimeric gapmers or comprise at least one modified internucleoside linkage, sugar moiety or nucleobase.

de Bruijn et al. teach the cDNA sequence encoding complement component c3 that is Genbank accession number K02765.

de Bruijn et al. do not teach inhibitors which specifically block complement component c3 expression or compounds that specifically hybridize to a nucleic acid molecule encoding complement component c3 wherein the compound can be a chimeric antisense oligonucleotide or an antisense oligonucleotide that comprises at least one modified internucleoside linkage, sugar moiety or nucleobase.

Carroll teaches that, "While the molecular events regulating C3 expression have not been identified, it seems most likely that inflammatory cytokines such as IL-la, IL-6, and IFN- as discussed above are involved (Figure 4)" (pg. 553).

Taylor et al. teach that antisense oligonucleotides 7-30 nucleotides long can be synthesized to inhibit the expression of any protein provided the cDNA sequence is known. Taylor *et al.* also indicate that making and using such oligos are available to those of ordinary skill in the art, that it is common practice to chemically modify the such oligonucleotides to prolong their bioactivity, and also teach that with software analysis and high affinity oligos, one needs to screen only 3-6 oligos to find one that inhibits its target 66-95% (p. 565).

Bennett et al. teach antisense compounds of 8-30 nucleobases in length, a method of making antisense that is specifically targeted to a nucleic acid molecule and

methods of treating cells *in vitro* with antisense of the invention (col. 5; line 55 to 65; col. 3, line 30 bridge to col. 4, line 57; col. 5, lines 25-32 and example 15). Bennett et al. teach the process for designing antisense oligonucleotides that target a particular nucleic acid and that this process includes determination of a site or sites within this gene for the oligonucleotide interaction to occur such that the desired effect, e.g., detection or modulation of expression of the protein, will result (col. 3, line 31 thru col. 4, line 57). Bennett et al. teach that, "Antisense compounds are commonly used as research reagents and diagnostics. For example, antisense oligonucleotides, which are able to inhibit gene expression with exquisite specificity, are often used by those of ordinary skill to elucidate the function of particular genes. Antisense compounds are also used, for example, to distinguish between functions of various members of a biological pathway. Antisense modulation has, therefore, been harnessed for research use" (col. 5, lines 25-35).

Baracchini et al. teach antisense of 8-30 nucleobases in length, a method of making antisense that is specifically targeted to a nucleic acid molecule and methods of inhibiting gene expression by delivering antisense to cells *in vitro* (cols. 6, line 35 bridge to col. 9, line 5; col. 9, lines 5-67; col. 17, example 3). Baracchini et al. also teach the process for designing antisense oligonucleotides that target a particular nucleic acid and that this process includes determination of a site or sites within this gene for the oligonucleotide interaction to occur such that the desired effect, e.g., detection or modulation of expression of the protein, will result (col. 9, line 5 thru col. 10, line 25).

It would have been obvious to one of ordinary skill in the art to use the known cDNA sequence of complement component c3 (as taught by de Bruijn et al.) to generate antisense sequences (as taught by Taylor et al.) to use for inhibition of complement component c3 expression in cells *in vitro* because antisense oligonucleotides, which are able to inhibit gene expression with exquisite specificity, are often used by those of ordinary skill to elucidate the function of particular genes (as taught by Bennett et al.) and could be used to identify the molecular events regulating C3 (as taught by Carroll). Further, it would have been obvious to one of ordinary skill in the art to incorporate modifications as taught by Baracchini *et al.* and Bennett *et al.* into said antisense compounds because these modifications were known and used in the art to confer desirable properties, such as enhanced nuclease resistance and cellular uptake, on antisense oligonucleotides.

One of ordinary skill in the art would have been motivated to practice a method of inhibiting the expression of complement component c3 in cells, comprising contacting the cells *in vitro* with an antisense compound targeted to a coding region of a complement component c3 locus because the cDNA sequence of the complement component c3 was known in the art and because Bennett et al. teach the use, by those of ordinary skill in the art, of antisense to elucidate the function of particular genes to distinguish between functions of various members of a biological pathway. One of ordinary skill in the art would have, therefore, been motivated to use antisense targeted to complement component c3 to elucidate the functions of complement component c3 and to distinguish those functions, thereby allowing identification the molecular events

regulating C3 in cells *in vitro* (as taught by Carroll). One would have been motivated to modify the antisense compounds above, as taught by Baracchini *et al.* and Bennett *et al.,* in order to increase cellular uptake, target affinity and resistance to degradation.

Finally, one of skill in the art would have a reasonable expectation of success of practicing the instantly claimed methods in cells *in vitro* given that Taylor teaches that with software analysis and high affinity oligos, one needs to screen only 3-6 oligos to find one that inhibits its target 66-95%, and since Baracchini *et al.* and Bennett *et al.* both teach making modified antisense compounds targeted to distinct regions of a target gene, the steps of which are routine to one of ordinary skill in the art.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

9. No claims are allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon B. Ashen whose telephone number is 571-272-2913. The examiner can normally be reached on Monday - Friday, 7:30 am - 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor, Andrew Wang can be reached on 517-272-0811811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Jba

J.D. SCHULTZ, Ph.D.
PATENT EXAMINER